REMARKS

Claims 1, 13-23, 25-33 and 37-52 are pending in this application. Claims 43-52 were withdrawn from consideration due to a non-elected status. Claims 27 and 30 were objected to due to informalities. Claims 1, 13-23, 25-30, 32, 33 and 37-42 were rejected under 35 U.S.C. § 112, first paragraph. Claims 1, 13-23, 25-33, 37-42 were variously rejected under 35 U.S.C. § 103.

Applicants expressly reserve the right to pursue prosecution of any presently excluded subject matter or claim embodiments in one or more future continuation and/or divisional application(s).

Applicants have carefully considered the points raised in the Office Action and believe that the Examiner's concerns have been addressed as described herein, thereby placing this case into condition for allowance.

Objections to Specification and Claims

The specification and claims 27 and 30 were objected to for allegedly failing to adhere to the requirements of the sequence rules. The Office stated that Applicants are required "to append SEQ ID Nos. to all mentions of specific amino acid sequences comprising four or more amino acids in the specification" and in the claims. Office Action, page 2.

Applicants respectfully point out that the sequences in claims 27 and 30 and on page 7, line 9, of the specification are nucleotide sequences, not amino acid sequences. Since these nucleotide sequences are less than ten nucleotides in length, SEQ ID Nos. are not required. 37 C.F.R. §1.821(a).

Accordingly, Applicants respectfully request withdrawal of the objections.

Rejections under 35 U.S.C. §112, first paragraph

Claims 1, 13-23, 25-30, 32, 33, and 37-42 were rejected under 35 U.S.C. §112, first paragraph, for allegedly not enabling any person skilled in the art to which it pertains, or with which

it is most nearly connected, to make and/or use the invention commensurate in scope with the claims. Applicants respectfully traverse this rejection.

The claimed invention is directed to a method of modulating an immune response to a second antigen through co-administration of (i) a complex comprising an immunomodulatory polynucleotide covalently conjugated to a first antigen and (ii) a second antigen. The immunomodulatory polynucleotide includes an immunostimulatory sequence (ISS) and the ISS comprises the sequence 5'-cytosine, guanine-3'. The complex and the second antigen are administered at the same site in the individual and the complex is administered in an amount sufficient to modulate an immune response in the individual to the second antigen. The claimed invention is also directed to a composition comprising (i) a complex including an ISS-containing immunomodulatory polynucleotide covalently conjugated to a viral conserved polypeptide antigen and (ii) a second antigen which is a viral variable polypeptide. The invention is also directed to a composition comprising (i) a complex including an an ISS-containing immunomodulatory polynucleotide covalently conjugated to an allergen and (ii) a second antigen.

The Examiner's concerns essentially relate to the effective "scope" of enablement, and whether the description and exemplary embodiments adequately support the invention as claimed to one of skill in the art. In particular, the Examiner states that "the specification, while being enabling for using an ISS molecule comprising SEQ ID NO:1, does not reasonably provide enablement for IS sequences that are shorter or do not conform to the enabled motif." Office Action, page 3. Applicants respectfully disagree with the assertion that the claimed methods are enabled only for a composition comprising SEQ ID NO:1.

In support of the rejection, the Examiner states that "there is no data presented in the specification that would indicate that any of the ISS molecules claimed (except for SEQ ID NO:1),

would be immunostimulatory when unclomplexed or complexed with another molecule. Although the claims require that the ISS molecules be immunostimulatory, see (i) of claim 1, there is no evidence provided in the disclosure that indicates that they are immunostimulatory." Office Action, page 4. The Examiner cites Fearon[1] as an example of the state of the art and asserts that "whether the genus of ISS polynucleotides claimed actually are immunostimulatory is unpredictable." Office Action, page 6.

In order to make a rejection, the Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F2d 1557, 27 USPQ2d 1510 (Fed. Cir. 1993); M.P.E.P. §2164.04. Applicants respectfully submit that the teachings of Fearon regarding the ISS sequence requirements for activity are not appropriate to support a lack of enablement in the present invention since Fearon teaches compositions other than those claimed.

As discussed in the response to an Office Action filed June 9, 2004, Fearon is focused on optimization and refinement of immunostimulatory sequence activity as opposed to identifying sequences with some, if not optimal activity. That the activity of a polynucleotide may be fine-tuned by sequence adjustments does not indicate a lack of enablement for the instant specification. Taken in its entirety, Fearon does not support the need for undue experimentation for the claimed invention. Indeed, the court found in *in re Wands* the enablement requirement met even though 4 of 9 antibodies analyzed (44%) were found to have the claimed binding requirements and those successful 4 were produced in only 2 of 10 fusion experiments. *In re Wands*, 858 F2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988).

[1] Fearon et al. (2003) European Journal of Immunology 33:2114-2122; "Fearon," of record.

Further, fulfillment of the enablement requirement does not require that every embodiment of the invention be predictable. Rather, unpredictability is permitted, the level of unpredictability permitted depending on the level of guidance provided by the specification and the knowledge in the art. Applicants respectfully note that the test for enablement is not whether a certain amount of experimentation is required to practice an invention, but rather whether the amount of experimentation is "undue." *In re Wands*, *Supra*, (Fed. Cir. 1988). Applicants respectfully submit that the specification has provided a reasonable amount of guidance to the skilled artisan with respect to the identification and testing of polynucleotide sequences with immunostimulatory activity and that the skilled artisan would be able to extend the teachings of the specification and the art to other immunostimulatory polynucleotides as claimed.

With regard to the state of the art, Applicants submit that immunostimulatory polynucleotides are well known in the art and respectfully note that polynucleotides with immunostimulatory sequences active in cells of many mammalian species have been described in scientific literature, including human, monkeys, chimpanzees, cows, swine, dogs, cats, rabbits, mice and rats. In particular, much has been described about ISS activity in human cells and immunostimulatory sequences active in human cells have been the subject of much scientific and patent literature. Thus, Applicants submit that the ISS art is more mature than the Examiner asserts.

In addition, the Office has recently issued claims directed to methods of treating a mammal, a subject or an individual through administering an immunostimulatory or immunomodulatory polynucleotide comprising an ISS, wherein the ISS comprises the sequence 5'-C, G-3'.[2] All of these patents have claimed priority dates earlier than or within seven months of the priority date of the instant application.

[2] See, for example, U.S. Pat. Nos. 6,613,751, 6,552,006, 6,534,062 and 6,498,148, submitted herewith.

The claims in these patents are supported with experiments in which a limited number of 5'-C, G-3' containing oligonucleotides were tested for a particular activity or effect in a mouse model and, in some cases, on human cells in culture. Thus, in these cases, the Office has apparently deemed the state of the art such that the task of identifying nucleotides surrounding the core 5'-C, G-3' motif as not an undue burden to the skilled artisan.

Applicants respectfully submit that the specification provides all the information required for one of skill in the art to make and use the invention to modulate the immune response to the second antigen as claimed. The specification teaches the requirements for the ISS and the immunomodulatory polynucleotide of the complex and provides methods by which ISS can be made and evaluated for immunomodulatory activity. See, for example, page 15, line 30, to page 21, line 17. The specification describes antigens and how to make the polynucleotide-antigen complexes for use in the invention. See, for example, page 21, line 20, to page 32, line 19. The specification provides guidance for the administration and formulations for administration of the claimed compositions. See, for example, page 39, line 30, to page 47, line 8. Finally, the specification provides methods to assess the modulation of the immune response as claimed. Such extensive disclosure provides adequate guidance such that a skilled artisan would be able to practice the invention without undue experimentation.

The court in *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988), found that the enablement requirement was satisfied by a "disclosure [that] provides considerable direction and guidance on how to practice [the] invention and presents working examples," in view of the fact that "[t]here was a high level of skill in the art at the time when the application was filed, and all of the methods needed to practice the invention were well known." *Id.* at 740. "Since one embodiment is ... disclosed in the specification, along with the general manner in which its current range was ascertained, ... other permutations of the invention could be practiced by those skilled in the art

without undue experimentation." *United States v. Telectronics, Inc.*, 857 F.2d. 788, 8 USPQ2d 1217 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989). Applicants respectfully submit that the specification provides a reasonable amount of guidance to the skilled artisan with respect to the direction in which the experimentation should proceed to optimize the teachings of the specification and the art and that any additional necessary experimentation is presumed to be within the level of ordinary skill in the art.

According to the Office, claims are not rejected as broader than the enabling disclosure under 35 U.S.C. §112 for noninclusion of limitations dealing with factors which must be presumed to be within the level of ordinary skill in the art; the claims need not recite such factors where one of ordinary skill in the art to whom the specification and claims are directed would consider obvious. M.P.E.P. §2164.08. The court has stated that "Enablement is not precluded by the necessity for some experimentation such as routine screening ...". *In re Wands*, 858 F2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). Applicants respectfully submit that varying the nucleic acid sequence of oligonucleotides and testing the oligonucleotides for immunostimulatory activity are well within the bounds of routine experimentation by one of skill in the art.

Thus, Applicants respectfully submit that the pending claims are in compliance with the enablement requirements and a *prima facie* case of lack of enablement has not been established.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. § 112, first paragraph.

Rejections under 35 U.S.C. §103

Claims 1, 13, 14, 17, 20-23, 25-33, 37, and 40-42 were rejected under 35 U.S.C. §103 as allegedly unpatentable over Schwartz, *et al.* (WO 98/55495, "Schwartz") or Carson, *et al.* (WO 98/16247, "Carson"), as further evidenced by Horner *et al.* (*Cellular Immunology,* 1998, 190:77-82,

"Horner") or Chu *et al.* (*J. Exp. Med.* 1997; 186:1623-1631, "Chu"). Claims 15 and 38 were rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Schwartz or Carson further evidenced by Horner or Chu and further in view of Lee *et al.* (*Ann. Med.* 30:460-468 (1998), "Lee"). Claims 16 and 39 were rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Schwartz or Carson further evidenced by Horner or Chu and further in view of Durali *et al.* (*J. of Virol.* 72:3547-3553 (1998), "Durali"). Claims 18 and 19 were rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Schwartz or Carson further evidenced by Horner or Chu and further in view of Anderson (US Patent No. 4,673,574). Applicants respectfully traverse this rejection.

These rejections rely heavily on the teachings of the primary references, Schwartz or Carson, which have been discussed during the prosecution of the instant application. The Office again points to the passage on page 12, lines 9-15, of Schwartz in support of this rejection. Although this passage describes in general terms, the administration of ISS in conjunction with one or more member of the listed group of immunomodulatory molecules, it certainly does not suggest the claimed method, i.e. co-admininstration of an ISS-first antigen conjugate and an unconjugated second antigen. Applicants respectfully point out that nothing in the remainder of Schwartz suggests co-admininstration of an ISS-first antigen conjugate and an unconjugated second antigen to modulate an immune response to the second antigen. Schwartz examines only the immune response to the antigen conjugated to the ISS or the immune response to the sole antigen administered in a mixture with the ISS.

Nothing in Schwartz or Carson provides motivation to the skilled artisan to administer an ISS-first antigen conjugate complex in an amount sufficient to modulate an immune response to a co-administered, but unconjugated, second antigen.

The present invention is based on the observed benefit of co-administration of an ISS-first antigen complex with a second antigen in the modulation of the immune response to the second antigen. Without an understanding of this benefit, one skilled in the art would have no motivation to undertake the claimed method. Both Schwartz and Carson demonstrate that conjugation of an

ISS molecule to an antigen is much more effective in stimulating an immune response to the antigen than administration of the antigen and ISS unconjugated in a mixture. Accordingly, based on the the knowledge in the art, the effective method to stimulate an immune response to an antigen is to administer the antigen in the form of an ISS-antigen conjugate rather than an ISS and antigen admixture.

Nothing in Schwartz or Carson, or in knowledge in the art, suggests that the benefit of conjugation to an ISS would be extended to a second, but unconjugated, antigen. Thus, the references provide no motivation for modifying the teaching therein to arrive at the claimed invention.

For reasons already of record, none of the secondary references provide what is missing from the primary reference, Schwartz or Carson. None of the references, either alone or in combination, describes or suggests modulating an immune response to a second antigen through co-administration of the second antigen and a complex comprising an immunomodulatory polynucleotide covalently conjugated to a first antigen. None of the references, either alone or in combination, describes or suggests the composition as claimed. Nothing in the references, or in the art, suggests that the benefit of conjugation to an ISS would be extended to the second, but unconjugated, antigen. Thus, the cited references do not provide an expectation of success of the claimed invention, i.e., a stimulation of an enhanced Th1 immune response to a second antigen when it is co-administered with an ISS-first antigen conjugate complex.

In sum, Applicants respectfully submit that a *prima facie* case of obviousness has not been made. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. §103(a).

CONCLUSION

Applicants believe that all issues raised in the Office Action have been properly addressed in this response. Accordingly, reconsideration and allowance of the pending claims is respectfully requested. If the Examiner feels that a telephone interview would serve to facilitate resolution of any outstanding issues, the Examiner is encouraged to contact Applicants' representative at the telephone number below.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 377882000800.

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Respectfully submitted,

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